

**METHODS AND COMPOSITIONS FOR TARGETED CLEAVAGE
AND RECOMBINATION**

ABSTRACT OF THE DISCLOSURE

5 Disclosed herein are methods and compositions for targeted cleavage of a genomic sequence, targeted alteration of a genomic sequence, and targeted recombination between a genomic region and an exogenous polynucleotide homologous to the genomic region.

10 The compositions include fusion proteins comprising a cleavage domain (or cleavage half-domain) and an engineered zinc finger domain, as well as polynucleotides encoding same. Fusion proteins comprising cleavage half-domains are used in pairs, to reconstitute a functional cleavage domain. In these fusion proteins, the zinc finger domain can be N-terminal to the cleavage half-domain, or the cleavage half-domain can be N-terminal to the zinc finger domain. The availability of

15 fusion endonucleases having these different polarities allows targeting (and thereby binding) of zinc finger endonucleases either to opposite strands of the DNA target or to the same strand of the DNA target, thereby increasing the number of possible sequences which can be targeted and cleaved by the fusion proteins.